Statement of True Translation

I, Kenichiro Akao, born January 26, 1967, Japanese Patent Attorney of the Tokyo IP Firm, Kyobashi-Nichiei Bldg. 4F, Kyobashi 3-chome 3-4, Chuo-ku, Tokyo, JAPAN, hereby declare that the submitted translation of Japanese Patent Application No. JP2004-064994 is an accurate translation from Japanese to English.

This 25th day of May 2009

By K. Akao

Kenichiro Akao

ASYMMETRIC REACTION CATALYST AND METHOD FOR PREPARING OPTICALLY ACTIVE NITROGEN-CONTAINING COMPOUND USING THE SAME

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001]

The present invention relates to an asymmetric reaction catalyst and a method for preparing an optically active nitrogen-containing compound. Preferably, the present invention relates to an asymmetric reaction catalyst and a method for preparing an optically active nitrogen-containing compound used in nucleophilic addition.

2. Description of the Related Art

[0002]

Asymmetric nucleophilic addition reactions to the unsaturated carbon of a C=C bond or C=N bond (for example, imine (C=N) or hydrazone (C=N-N) compound) in the presence of a Lewis acid catalyst results in the formation of a new carbon-carbon bond. These reactions have been heavily examined because they can be used in the synthesis of various optically active nitrogen-containing compounds. Also, from the viewpoints of selectivity and stability, various metals and ligands are used as the above-mentioned catalyst.

The inventors of the present invention have already developed an asymmetric catalyst prepared from a zirconium alkoxide and a binaphthol derivative and have reported that asymmetric Diels-Alder reactions (for example, refer to patent Reference 1), aldol reactions (for example, refer to patent Reference 2 and Non-patent Reference 1) and imino aldol reactions (for example, refer to patent Reference 3) can be carried out with high yields and high stereoselectivity.

Also, it is expected that niobium has a high Lewis acidity (for example refer to Non-patent Reference 2) and an example of an asymmetric Diels-Alder reaction carried out using niobium in the catalyst has been reported (for example, refer to Non-patent Reference 3).

[0003]

[patent Reference 1]

Japanese Patent Laid-open Publication 2002-356454

[patent Reference 2]

Japanese Patent Laid-open Publication 2000-67833

[patent Reference 3]

Japanese Patent Laid-open Publication H11-33407

[Non-patent Reference 1]

Yamashita et al., *J. Am. Chem. Soc.*, 2002, Vol. 124, page 3292

[Non-patent Reference 2]

C. Andrade, *Tetrahedron Lett.*, 2001, Vol. 42, page 6473

[Non-patent Reference 3]

J. Howarth and K. Gillespie, *Molecules*, 2000, Vol. 5, page 993

SUMMARY OF THE INVENTION

[0004]

However, effective catalysts are desired for the purpose of developing more effective reactions, in other words, reactions having chemical yields close to 100% and stereoselectivity close to 100%.

An object of the present invention is to solve the above-mentioned problem by providing an asymmetric reaction catalyst which achieves superior yields and superior stereoselectivity as well as being easy to handle and by also providing a method for preparing an optically active nitrogen-containing compound using the same.

[0005]

The inventors have found that an asymmetric catalyst having niobium as the active central metal can be obtained by mixing a niobium compound and a triol having an optically active binaphthol derivative. Also, the inventors have found that this catalyst is suitable for asymmetric nucleophilic addition reactions.

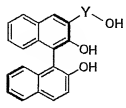
[0006]

The asymmetric reaction catalyst of the present invention is obtained by mixing a pentavalent niobium compound and a triol having an optically active binaphthol derivative of R or S configuration. Preferably, the above-mentioned niobium

compound is represented by the formula NbX_5 (wherein, X represents an alkoxide or a halogen atom).

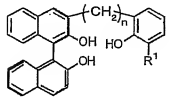
[0007]

Preferably, the above-mentioned triol is represented by the following formula (I):



(I)

(wherein, Y represents a divalent hydrocarbon group) or is represented by the following formula (II):



(II)

(wherein, R^1 represents a hydrogen atom or a hydrocarbon group having 1 to 4 carbons; and n is an integer from 0 to 2).

[0008]

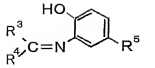
Preferably, the asymmetric reaction catalyst of the present invention further comprises an imidazole derivative and/or molecular sieves.

[0009]

In the method for preparing a optically active nitrogen-containing compound of the present invention, a reaction substrate represented by $R^3R^4C{=}N{\cdot}Z$ (wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^5 represents a hydrogen atom or a trifluoromethyl group)and a nucleophilic agent are reacted by nucleophilic addition using the above-mentioned asymmetric reaction catalyst.

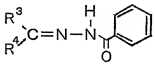
[0010]

Preferably, the above-mentioned reaction substrate is an imine represented by the following formula (III):



(III)

(wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^5 represents a hydrogen atom or a trifluoromethyl group) or the above-mentioned reaction substrate is a benzoylhydrazone represented by the following formula (IV):

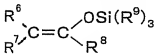


(IV)

(wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group).

[0011]

Preferably, the above-mentioned nucleophilic agent is a silicon enolate represented by the following formula (V):



(V)

(wherein R^6 and R^7 are each independently one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, and an aromatic hydrocarbon group; R^8 is one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an alkoxy group, and an alkylthio group; and each R^9, being the same or different, represents a hydrocarbon group).

[0012]

In accordance with the present invention, an asymmetric reaction catalyst which achieves superior yields and superior stereoselectivity as well as being easy to handle can be obtained. Also, an optically active nitrogen-containing compound can be efficiently prepared by an asymmetric nucleophilic addition reaction using this catalyst. Furthermore, a selective reaction can be carried out without the occurrence of side reactions because the reaction is mild.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a reaction scheme in order to prepare a triol having a binaphthol Derivative.

DETAILED DESCRIPTION OF THE INVENTION

[0013]

The embodiments of the present invention will now be explained.

<Niobium Compound>

There are no particular limitations as to what can be used as the pentavalent niobium compound in the present invention. Examples include compounds represented by the formula NbX_5 (wherein, X is an alkoxide or a halogen atom). Among these, from the viewpoint of ease of handling, Nb alkoxides (in particular, Nb methoxide or Nb ethoxide) are preferable.

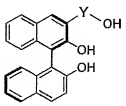
[0014]

<Triol Having a Binaphthol Derivative>

The triol having a binaphthol derivative used in the present invention coordination-bonded to niobium which is the active central metal, and becomes a ligand by mixing this triol with the above-mentioned niobium compound. Further, this ligand has a catalytic activity as a whole. In this triol, binaphthol derivative part consists of R configuration or S configuration, and shows an optical activity. Therefore, the triol becomes an asymmetric ligand and functions as an asymmetric catalyst.

[0015]

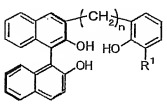
For example, a compound represented by the following formula (I):



(I)

(wherein, Y represents a divalent hydrocarbon group) or a compound represented by

the following formula (II):



(II)

(wherein, R^1 represents a hydrogen atom or a hydrocarbon group having 1 to 4 carbons; and n is an integer from 0 to 2) can be suitably used as the above-mentioned triol.

[0016]

Specific examples of formula (II) include triols wherein, R^1 is one selected from the group consisting of H, Et, i-Pr(isopropyl group), and t-Bu(tert-butyl) and n = 0 or 1.

[0017]

<Preparation of the Catalyst>

The mixed ratio of the above-mentioned niobium compound and the above-mentioned triol is preferably 1/1 to 1/2 (niobium compound/triol) and more preferably 1/1 to 1/1.3.

There are no particular limitations to the method for mixing the above-mentioned niobium compound and the above-mentioned triol. Normally, the above-mentioned compounds can be mixed in an organic solvent and arbitrarily stirred. Hydrocarbons and halogenated hydrocarbons can be suitably used as the organic solvent. In particular, methylene chloride, toluene, or their mixture is suitable. There are no particular limitations to the mixing temperature. It is easy to mix close to room temperature and then it is suitable to heat to a temperature between room temperature and the boiling point of solvent(preferably around 60°C) for aging. The heating time of the catalyst is normally in the range from 30 minutes to 24 hours and preferably in the range from 1 to 3 hours.

[0018]

<Other Components>

If a nitrogen-containing compound is further added to the above-mentioned niobium compound and the triol, the catalytic properties become better. Preferably, the nitrogen containing compound is an imidazoles, especially an N-methylimidazole.

It is preferable that the amount of the imidazoles added is approximately the same number of moles as the above-mentioned niobium compound. It is preferable that the imidazoles are added after the triol and the niobium compound are mixed or are added before the addition of the nucleophilic agent to the reaction substrate.

Also, the catalytic properties can be improved by further adding molecular sieves to the above-mentioned niobium compound and the above-mentioned triol. Molecular sieves is an aluminosilicate synthetic crystalline zeolite, and has a specific adsorption property. There exists a standard(for example, 3A-5A,10A) to represent an internal diameter of the cavity of molecular sieves, and normally, 3A is suitable. The amount of molecular sieves is preferably within a range of mixing and agitating the above-mentioned niobium compound and the triol without trouble. Normally, 10-200mg of molecular sieves per 1 ml of organic solvent is added and 50-100mg is suitable.

[0019]

<Reaction Substrate>

The catalyst of the present invention which has been prepared as above has a catalytic action for any asymmetric reaction. From the viewpoint of yield and stereoselectivity, the catalyst of the present invention is preferably used in an asymmetric reaction wherein a nucleophilic agent is added to the following reaction substrate. An optically active nitrogen-containing compound is reacted by this asymmetric reaction.

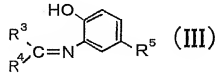
Examples of the reaction substrate include compounds represented by $R^3R^4C=N-Z$(wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, a hetero atom, and a hydrocarbon group having a functional group and Z represents an aryl group or an acylamino group). These compounds are collectively termed imines or imines and acylhydrazones.

Imines or acylhydrazones are suitable for the reaction substrate mentioned above. When these compounds are used, R^3 and R^4 in the above-mentioned formula are each independently one selected from the group consisting of a saturated or an unsaturated aliphatic hydrocarbon group, and an aromatic hydrocarbon group. These substituents may have one of a chain structure, a circular structure, a heterocyclic structure, or a heteroatom. And when these compounds are used, a

functional group as R^3 or R^4 does not restricted unless which inhibits the addition reaction. Examples of the functional group include a halogen atom, an ester group, a nitro group, an ether group, and an amide group.

[0020]

Examples of the imine mentioned above include an imine represented by the following formula (III):

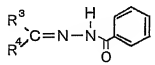


(III)

(wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, a hetero atom, and a hydrocarbon group having a functional group and R^5 represents a hydrogen atom or a trifluoromethyl group).

[0021]

Examples of the acylhydrazone mentioned above include a benzoylhydrazone represented by the following formula (IV):



(IV)

(wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group).

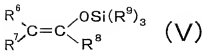
[0022]

Each type of imine compound mentioned above can be easily synthesized by the corresponding aldehyde and amine following an already known method. Similarly, each type of acylhydrazone compound mentioned above can be easily synthesized from the corresponding acylhydrazine following an already known method.

[0023]

(Nucleophilic Agent)

A silicon enolate(silyl enolate) represented by the following formula (V):



(V)

(wherein R^6 and R^7 are each independently one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, and an aromatic hydrocarbon group; R^8 is one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an alkoxy group, and an alkylthio group; and each R^9, being the same or different, represents a hydrocarbon group), or an allylsilane, hydrogen cyanide, and so on can be suitably used as the nucleophilic agent when the present catalyst is used in an asymmetric nucleophilic addition reaction. When the above-mentioned compound ($R^5R^4C=N-Z$) is the reaction substrate and a silicon enolate is used as the nucleophilic agent, an optically active β-aminocarbonyl compound(for example, R^5 of formula (V) = a hydrocarbon group) or an optically active β-amino acid derivative(for example, R^5 of formula (V) = an alkoxy group or a sulfide group) can be obtained. And, when a allylsilane compound is used as the nucleophilic agent, an optically active homoallylic amine derivative can be obtained, and when a cynide is used as the nucleophilic agent, an optically active α -amino nitrile derivative can be obtained.

[0024]

<Addition of the reaction substrate >

There are no particular limitations to the method for adding the reaction substrate to the above-mentioned catalyst.

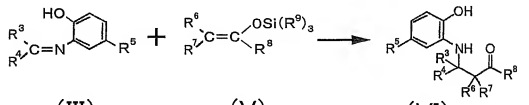
Generally, the imine(an imine and a silicon enolate are both reaction substrates), which has been dissolved in a solvent, is added dropwise to a solution including the above-mentioned catalyst and a solution including the nucleophilic agent may then be added dropwise. The reaction temperature can by arbitrarily selected according to the type of reaction substrate. Normally, the temperature is -78°C to room temperature and preferably -40°C to 0°C. The reaction time is generally 1 to 72 hours. The concentration of the reaction substrate in the reaction system including the above-mentioned catalyst and solvent is preferably 0.05 to 1.0 mol/l and more preferably 0.1 to 0.5 mol/l.

For example, after an imine(hydrazone) compound dissolved in a halogen hydrocarbon

such as methylene chloride is added dropwise to the solution containing the above-mentioned catalyst, the nucleophilic agent(a solution of a silyl enolate) may then be added dropwise.

[0025]

When the catalyst of the present invention is used in an asymmetric reaction in which the above-mentioned nucleophilic agent is nucleophilically added to the above-mentioned reaction substrate, very high enantioselectivity is shown and various amine compounds can be obtained in high optical purity. For example, a β-aminoketone (right-hand side formula (VI)) in the above-mentioned formula) with at least 70% chemical yield and at least 90% optical yield can be obtained in most situations by the Mannich reaction represented by the following reaction formula:



(III) (V) (VI)

. The compounds of formula (III) and (V) in the left-hand side of the above-mentioned formula are an imine compound and a silicon enolate, respectively, already shown by chemical formulas. The contents represented by reference symbols such as R^3 are as already mentioned.

[0026]

Below, the present invention will be specifically explained using examples and comparative examples. However, these do not limit the present invention.

1. Experiment 1

[Example 1]

[0027]

<Preparation of Triol Having Binapthol derivative>

A triol was prepared in accordance with the reaction formula shown in Fig. 1.

Firstly, sodium hydride (275 mmol) was suspended in tetrahydrofuran (THF) (120 ml) and to this, 2-isopropylphenol (111 mmol, reference symbol A1 in Fig. 1) dissolved in THF (30 ml) was added dropwise at 0°C. After 30 minutes, chloromethyl

methyl ether (221 mmol) was added to this solution and after heating to room temperature, the reaction was stopped by adding methanol and then water. The aqueous phase was extracted with ether. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried using anhydrous sodium sulfate. The solvent was distilled off under reduced pressure from the dry substance. The residue was purified by silica gel chromatography to obtain 1-isopropyl-2-methoxy methoxybenzene (17.5 g, 87% yield, reference symbol A2 in Fig. 1).

[0028]

At -78°C, a hexane solution of n-butyl lithium (100 mmol/64 ml) was added dropwise to a THF (200 ml) solution including 15.0 g (83 mmol) of the above-mentioned compound A2 and 100 g(53 mmol) of tetramethylethylenediamine (TMEDA). After 30 min, the mixed solution was heated to 0°C, stirred for 1 hour, and again cooled to -78°C. Dimethylformamide (DMF) (15.9 ml) was then added dropwise. After the reaction solution was slowly heated to room temperature, the reaction solution was poured into a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with ether. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried using anhydrous sodium sulfate. The solvent was distilled off under reduced pressure from the dry substance. The residue was purified by silica gel chromatography to obtain 3-isopropyl-2-methoxy methoxybenzaldehyde (12.9 g, 74% yield, reference symbol A3 in Fig. 1).

^{1}H-NMR of product A3 δ(ppm): 1.25 (d, 6H, J = 7.1 Hz), 3.40 (sept, 1H, J = 7.1 Hz), 3.60 (s, 3H), 5.06 (s, 1H), 7.25 (dd, 1H, J = 7.6, 7.6 Hz), 7.55 (dd, J = 1.7, 7.6 Hz), 7.70 (dd, 2H, J = 1.7, 7.6 Hz), 10.3 (s, 1H)

[0029]

Next, after a hexane solution of n-butyl lithium (45.4 mmol/28.9 ml) was added dropwise at room temperature to an ether (450 ml) solution containing (R)-2,2'-bis(methoxymethoxy)-[1,1']binaphthalene (37.9 mmol, reference symbol A4 in Fig. 1) and TMEDA (45.1 mmol), the solution was stirred for 1.5 hours. After the mixed solution was cooled to -78°C, an ether (50 ml) solution of the above-mentioned product A3 (22.9 mmol) was added dropwise. After the reaction solution was slowly heated to

room temperature, the reaction solution was poured into a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with ether. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried using anhydrous sodium sulfate. The solvent was distilled off under reduced pressure from the dry substance. The residue was purified by silica gel chromatography to give approximately a 1:1 diastereomeric ratio of (R)-(2,2'-dimethoxy-methoxy-[1,1']binaphthyl-3-yl)-(3-isopropyl-2-methoxymethoxyphenyl)methanol (12.2 g, 92% yield, reference symbol A5 in Fig. 1).

[0030]

Under ice-cooling, hydrogen chloride-saturated methanol (35 ml) was added to a dichloromethane (35 ml) solution of the above-mentioned product A5 (21 mmol) and stirred for 2 hours. The mixed solution was neutralized by the addition of a saturated aqueous solution of sodium hydrogen carbonate and the organic phase was separated. The aqueous phase was extracted with methylene chloride. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and dried using anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure from the dry substance. At 0°C, triethylsilane (67.2 mmol) was added to a methylene chloride (100 ml) solution of the obtained crude alcohol (A6 in Fig. 1). Next, a boron trifluoride-ether complex (65.1 mmol) was added dropwise. After the reaction solution was stirred overnight, the reaction solution was neutralized by adding a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was separated. The remaining aqueous phase was extracted with methylene chloride. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried with anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography to give the final product [(R)-3-(2-hydroxy-3-isopropylbenzyl)-[1,1']binaphthalene 2,2'-diol] (6.2 g, 68% yield, 2 steps, reference symbol A7 in Fig. 1, here R^1 is i-Pr group). In addition, MOM in Fig. 1 represents a methoxymethoxy group.

[0031]

^{1}H-NMR of product A7 δ (ppm): 1.20 (d, 3H, J = 6.8 Hz), 1.21 (d, 3H, J = 6.8

Hz), 3.25 (sept, 1H, J = 6.8 Hz), 4.17 (d, 1H, J = 14.9 Hz), 4.23 (d, 1H, J = 14.9 Hz), 4.99 (s, 1H), 5.63 (s, 1H), 6.51 (s, 1H), 6.90 (ddd, 1H, J = 1.5, 7.5, 7.5 Hz), 7.08-7.11 (m, 3H), 7.22-7.39 (m, 6H), 7.82 (d, 1H, J = 7.9 Hz), 7.88 (d, 1H, J = 8.1 Hz), 7.93 (s, 1H), 7.97 (d, 1H, J = 9.0 Hz)

^{13}C-NMR ($CDCl_3$) of product A7 δ (ppm): 22.5, 22.8, 27.1, 31.5, 108.9, 110.6, 111.5, 117.8, 120.6, 124.1, 124.2, 124.5, 124.9, 125.9, 127.1, 127.6, 128.0, 128.1, 128.5, 128.8, 129.5, 129.9, 131.2, 131.7, 132.2, 133.2, 135.8, 149.8, 151.1, 152.8.

(here R^1 of A7 in Fig. 1 is isopropyl group (i-Pr) similar to A5, A6).

[0032]

Specific rotation($[\alpha]_D^{30}$), melting point(Mp), and infrared absorption(IR) spectrum of product A7 is as follows.

$[\alpha]_D^{30}$: +63.6 (c 1.03, THF)

Mp: 205-206°C

IR (KBr): 3505, 3425, 1592, 1463, 820, 751 cm^{-1}

The NMR spectra (^{1}H-NMR, ^{13}C-NMR) were measured using JEOL-LA300 or JEOL-LA500 (NMR (nuclear magnetic resonance) spectrometers manufactured by JEOL Ltd.). Optical rotation was measured using JASCO P-1010 (polarimeter manufactured by JASCO Corporation). The IR spectra were measured using FT/IR-610 (Fourier transform IR spectrometer manufactured by JASCO Corporation).

[0033]

<Asymmetric Nucleophilic Addition Reaction of a Ketene Silyl Acetal to an Aldimine Using an Asymmetric Reaction Catalyst>

1. Preparation of Reaction Substrate and Nucleophilic Agent

The imine (aldimine) prepared by recrystallizing the product prepared from the corresponding aldehyde and phenol derivative in dichloromethane and DMF and also in the presence of molecular sieves was used as the reaction substrate. The silyl enolate (silyl enol ether) was synthesized according to the method disclosed by S. Kobayashi et al. in "Silyl Enol Ethers", in *Science of Synthesis: Houben-weyl Methods of Molecular Transformations*, George Thieme Verlag, Stuttgart, 2002, Vol. 4, p. 317. The other chemicals used in the reaction were all purchased commercial products and were purified according to necessity. The reaction was completely performed under an argon atmosphere.

[0034]

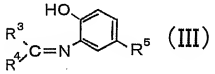
2. Preparation of Catalyst

The above-mentioned product A6 (72 μmol) was dissolved in toluene (0.3 ml). To this solution was added a toluene (0.6 ml) solution of N-methylimidazole (NMI) (60 μmol) at room temperature and stirred. After this mixed solution was stirred for 10 min, a toluene (0.6 ml) solution of $Nb(OMe)_5$ (60 μmol)was added. After heating to 60°C and stirring for 3 hours, the mixed solution was then returned to room temperature. This mixed solution was transferred to a flask having molecular sieves 3A (100 mg) and after being washed with methylene chloride (0.5 ml), was stirred for 30 minutes.

[0035]

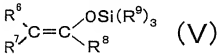
3. Asymmetric Reaction

The above-mentioned solution was cooled to -20°C and a methylene chloride (0.7 ml) solution of the imine represented by the following formula III:



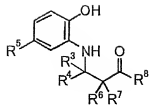
(III)

(0.6 mmol, R^3 = Ph, R^4 = H, R^5 = H)and then a methylene chloride (0.3 ml) solution of the silyl enol ether represented by the following formula V:



(V)

(0.72 mmol, R^6 = R^7 = R^9 = Me, R^8 = OMe) were added. After stirring for 48 hours, the reaction was stopped by pouring the reaction solution into a saturated aqueous solution of sodium hydrogen carbonate. The aqueous phase was extracted with methylene chloride. The above-mentioned aqueous phase and organic phase were combined, washed with water and a saturated sodium chloride solution in that order, and then dried with anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure from the dry substance. The obtained crude product was purified using preparation thin layer chromatography (benzene/ethyl acetate = 9/1) and an aminoketone derivative represented by the following formula (VI):



was obtained (yield 86%, R^3 to R^8 = same as in the above-mentioned formulas III and V). The asymmetric yield (99% ee) of the product VI was determined by HPLC (high-performance liquid chromatography) using a chiral column.

[0036]

Various Properties of Products VI

Name: (S)-methyl 2,2'-dimethyl-3-(2-hydroxyphenyl)amino-3-phenylpropionate

IR (KBr): 3401, 1709, 1611, 1514, 1453, 1391 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.21 (s, 3H), 1.24 (s, 3H) 3.68 (s, 3H), 4.57 (s, 1H), 6.36-6.76 (m, 4H), 7.21-7.28 (m, 5H).

^{13}C-NMR ($CDCl_3$): δ 19.9, 24.2, 47.3, 52.1, 64.3, 113.2, 114.1, 117.6, 120.8, 127.3, 127.9, 128.3, 135.6, 138.9, 144.0, 178.0.

HPLC (Daicel Chiralpak AD, hexane/^{i}PrOH = 9/1, flow rate = 1.0 ml/min, t_R = 9.3 min (3R), t_R = 16.0 min (3S). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. found: C, 72.28; H, 7.20; N, 4.62.

High resolution mass spectroscopy(HRMS): Calcd for $C_{18}H_{21}NO_3$ (M^+) 299.1522, found 299.1497.

Absolute configuration of S-configuration of product VI: determined by X-ray crystal structure analysis of the corresponding camphor acid ester.

[0037]

<Examples 2 to 10>

In each of the compounds in the above-mentioned formulas III and V, apart from R^3 to R^9 being changed to the products shown in Table 1, the reactions were performed the same as in Example 1. The chemical yields and asymmetric yields of the compounds are shown in Table 1.

[0038]

Table 1

	Formula (III) Imine			Formula (IV) Ketene Silyl Acetal				Reaction Product Yields (%)	
	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Chemical Yield	Asymmetric Yield
Example 1	H	Ph	H	Me	Me	OMe	Me	86	99% ee
Example 2	H	(4-Cl)C_6H_4	H	Me	Me	OMe	Me	82	98% ee
Example 3	H	(4-OMe)C_6H_4	H	Me	Me	OMe	Me	79	96% ee
Example 4	H	1-Naphthyl	H	Me	Me	OMe	Me	40	95% ee
Example 5	H	2-Naphthyl	H	Me	Me	OMe	Me	77	98% ee
Example 6	H	3-Thienyl	H	Me	Me	OMe	Me	85	93% ee
Example 7	H	Ph	CF_3	Me	Me	OMe	Me	75	91% ee
Example 8	H	Ph	H	H	H	SEt	Me	69	84% ee
Example 9	H	(4-Cl)C_6H_4	H	H	H	SEt	Me	44	88% ee
Example 10	H	2-Furyl	H	H	H	SEt	Me	70	87% ee

[0039]

As shown in Table 1, when an imine was used in the reaction substrate of each of the Examples, a high asymmetric yield of approximately 90% of the corresponding β-aminoketone derivative was obtained by an asymmetric nucleophilic addition reaction using silyl enolate as the nucleophilic agent. Thus, it was understood that a nucleophilic reaction having high enantioselectivity to an imine is possible.

[0040]

The properties of the reaction products (aminoketone derivatives) obtained in Examples 2 to 10 are shown below.

[0041]

<Example 2>

(S)-methyl 3-(4-chlorophenyl)-2,2'-dimethyl-(2-hydroxyphenyl)aminopropionate

IR (KBr) 3359, 1709, 1610, 1513, 1490, 1450, 738 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.19 (s, 3H), 1.24 (s, 3H) 3.67 (s, 3H), 4.55 (s, 1H), 6.31-6.90 (m, 4H), 7.22 (s, 2H), 7.35 (s, 2H).

^{13}C-NMR ($CDCl_3$): δ 20.2, 24.7, 47.3, 52.4, 64.0, 113.3, 114.3, 117.9, 121.1, 128.2, 128.3, 129.7, 133.2, 135.4, 137.7, 144.0, 177.5.

HPLC: measuring conditions same as Example 1, t_R = 8.3 min (3R), t_R = 16.7 min (3S).

Anal. Calcd for $C_{18}H_{20}NO_3Cl$: C, 64.77; H, 6.04; N, 4.20. found: C, 64.47; H, 6.18; N, 4.01.

HRMS: Calcd for $C_{18}H_{20}NO_3Cl$ (M^+) 333.1133, found 333.1109.

[0042]

<Example 3>

Methyl 2,2'-dimethyl-3-(2'-hydroxyphenylamino)-3-(4'-methoxyphenyl)propionate

IR (neat): 3420, 2979, 1715, 1612, 1510, 1252 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.20 (s, 3H), 1.22 (s, 3H), 3.68 (s, 3H), 3.76 (s, 3H), 4.50 (s, 1H), 6.39 (d, 1H, J = 7.9 Hz), 6.35 (dd, 1H, J = 7.6, 7.6 Hz), 6.62 (dd, 1H, J = 7.6, 7.6 Hz), 6.68 (d, 1H, J = 7.9 Hz), 6.81 (d, 1H, J = 8.5 Hz), 7.19 (d, 1H, J = 8.5 Hz).

^{13}C-NMR ($CDCl_3$): δ 20.1, 24.4, 47.5, 52.2, 55.2, 64.2, 113.4, 114.3, 115.3, 117.2, 118.1, 119.7, 121.1, 129.4, 131.0, 135.6, 144.4, 158.8, 177.8.

HPLC: measuring conditions same as Example 1, t_R = 11.1 min (3R), t_R = 28.0 min (3S).

HRMS: Calcd for $C_{19}H_{23}NO_4$ (M^+) 329.1627, found 329.1638.

[0043]

<Example 4>

(S)-methyl 2,2'-dimethyl-3-(2-hydroxyphenyl)amino 3-(1'-naphthyl)-propionate

^{1}H-NMR ($CDCl_3$): δ 1.18 (s, 3H), 1.25 (s, 3H) 3.66 (s, 3H), 5.62 (s, 3H), 6.28-6.62 (m, 4H), 7.22-8.00 (m, 7H).

^{13}C-NMR ($CDCl_3$): δ 19.9, 25.1, 48.4, 52.4, 57.8, 113.4, 114.2, 117.9, 121.2, 122.1, 123.2, 125.2, 125.3, 125.4, 126.1, 128.1, 129.1, 133.6, 135.3, 144.1, 177.9.

HPLC: apart from using chiralcel AD in the column, measuring conditions same as Example 1, t_R = 14.6 min (3s), t_R = 10.6 min (3R).

Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. found: C, 75.48; H, 6.49; N, 3.94.

HRMS: Calcd for $C_{18}H_{20}NO_3Cl$ (M^+) 349.1678, found 349.1668.

[0044]

<Example 5>

Methyl 2,2'-dimethyl-3-(2'-hydroxyphenyl)amino-3-(2'-naphthyl)propionate

IR (KBr) 3418, 1710, 1610, 1510, 1270, 736 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.26 (s, 3H), 1.29 (s, 3H), 3.70 (s, 3H), 4.71 (s, 1H), 6.40-6.70 (m, 4H) 7.41-7.46 (m, 3H), 7.75-7.81 (m, 4H).

^{13}C-NMR ($CDCl_3$): δ 20.2, 24.5, 47.6, 52.3, 64.8, 114.0, 114.3, 118.0, 121.1, 125.8, 126.2, 127.5, 127.6, 127.6, 127.9, 132.9, 133.0, 135.5, 136.7, 144.3, 177.7.

HPLC: apart from the flow rate being 0.8 ml/min, measuring conditions same as Example 1, t_R = 12.2 min (3R), t_R = 26.0 min (3S).

HRMS: Calcd for $C_{22}H_{23}NO_3$ (M^+) 349.1678, found 349.1671.

[0045]

<Example 6>

(R)-methyl 3-(2-hydroxyphenyl)amino-2,2'-dimethyl-3-(3'-thienyl)propionate

IR (neat) 3413, 2978, 1708, 1608, 1513, 1446, 1267, 1192, 1140, 741 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.25(s, 3H), 1.28(s, 3H), 3.69(s, 3H), 4.66(s, 1H), 6.46-6.71 (m, 4H), 6.98(d, 1H J= 5.6 Hz), 7.06(s, 1H), 7.21(s, 1H).

^{13}C-NMR ($CDCl_3$): δ 20.4, 24.1, 47.2, 52.2, 61.2, 114.5, 115.1, 118.9, 121.1, 122.9, 125.2, 127.3, 135.3, 140.7, 145.0, 177.7.

HPLC: measuring conditions same as Example 1, t_R = 9.2 min (3S), t_R = 14.3 min (3R).

[0046]

<Example 7>

(S)-methyl 3-(2-hydroxy-5-trifluoromethylphenyl)amino-2,2'-dimethyl-3-phenylpropionate

IR (neat) 1707, 1612, 1531, 1442, 1336, 1277, 1115 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.22 (s, 3H), 1.26 (s, 3H), 3.70 (s, 3H), 4.54 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H, J = 7.6 Hz), 7.23-7.32 (m, 5H).

^{13}C-NMR ($CDCl_3$): δ 20.2, 24.7, 47.3, 52.4, 64.5, 109.9, 113.6, 115.0, 123.2, 123.5, 127.8, 128.2, 135.7, 138.3, 137.0, 146.6, 177.9.

HPLC: measuring conditions same as Example 1, t_R = 5.4min (3R), t_R = 7.3 min (3S).

Anal. Calcd for $C_{19}H_{20}F_3NO_3$: C, 62.12; H, 5.49; F, 15.11; N, 3.81; O, 13.07. found: C, H, N.

[0047]

<Example 8>

(S)-S-ethyl 3-(2-hydroxyphenyl)amino-3-phenylpropanthioic acid

IR (KBr) 3396, 1647, 1608, 1520, 1449, 1362 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.67 (t, 3H, J = 7.3 Hz), 2.83 (q, 2H, J = 7.3 Hz), 2.97 (dd, 1H, J = 5.4, 14.9 Hz), 3.07 (dd, 1H, J = 8.1, 14.9 Hz), 4.81 (dd, 1H, J = 5.4, 8.1 Hz), 6.44-6.71 (m, 4H), 7.20-7.33 (m, 5H).

^{13}C-NMR ($CDCl_3$): δ 14.4, 23.6, 51.4, 56.1, 114.4, 114.6, 118.8, 121.1, 126.3, 127.4, 128.6, 134.9, 141.7, 144.7, 198.4.

HPLC: apart from using chiralpak AS in the column and hexane/^{i}PrOH = 19/1, measuring conditions same as Example 1, t_R = 26.6 min (3S), t_R = 38.2 min (3R). Anal. Calcd for $C_{17}H_{18}NO_2S$: C, 67.74; H, 6.35; N, 4.65. found: C, 68.00; H, 6.54; N, 4.54.

HRMS: Calcd for $C_{17}H_{19}NO_2S$ (M^+) 301.1138, found 301.1102.

[0048]

<Example 9>

(S)-S-ethyl 3-(4'chlorophenyl)-3-(2-hydroxyphenyl)amino-phenylpropanthioic acid

IR (neat) 3412, 1665, 1516, 1447, 742 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.21 (t, 2H J = 7.4 Hz), 2.83 (q, 2H J = 7.4 Hz), 2.96 (dd, 1H, J = 5.1, 14.9 Hz), 3.05 (dd, 1H, J = 8.3, 14.9 Hz), 4.78 (dd, 1H, J = 5.1, 8.3 Hz), 6.39-6.78 (m, 4H), 7.22-7.28 (m, 5H).

^{13}C-NMR ($CDCl_3$): δ 14.5, 23.7, 51.2, 55.6, 114.5, 115.0, 119.3, 121.2, 127.8, 128.9, 133.2, 134.6, 140.3, 144.7, 197.8.

HPLC: measuring conditions same as Example 1, t_R = 19.5 min (3S), t_R = 24.3 min (3R). Anal. Calcd for $C_{17}H_{18}NO_2ClS$: C, 60.80; H, 5.40; N, 4.17. found: C, 60.85; H, 5.60; N, 3.99.

HRMS: Calcd for $C_{17}H_{18}NO_2ClS$ (M^+) 335.0747, found 335.9758.

[0049]

<Example 10>

(S)-S-ethyl 3-(2'-furyl)-3-(2-hydroxyphenyl)amino-phenylpropanthioic acid

IR (neat) 3414, 1674, 1608, 1513, 1448, 1349, 740 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.32 (t, 3H, J = 7.3 Hz), 2.90 (q, 2H, J = 7.3 Hz), 3.06 (dd, 1H, J = 5.4, 15.6 Hz), 3.19 (dd, 1H J = 8.3, 15.6 Hz), 4.81 (dd, 1H J = 5.4, 8.3 Hz), 6.11 (d, 1H J

= 3.2 Hz), 6.26 (dd, 1H J = 2.0, 3.2 Hz), 6.60-6.81 (m, 4H), 7.35 (d, 1H J = 2.0 Hz).

^{13}C-NMR ($CDCl_3$): δ 14.5, 23.6, 48.0, 50.8, 106.8, 110.2, 115.0, 118.0, 120.7, 121.5, 133.8, 142.0, 147.1, 153.8, 198.2.

HPLC: measuring conditions same as Example 4, t_R = 15.4 min (3S), t_R = 8.9 min (3R).

Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. found: C, 61.86; H, 5.72; N, 4.80.

HRMS: Calcd for $C_{15}H_{17}NO_3S$ (M^+) 291.0932, found 291.0931.

WHAT IS CLAIMED IS:

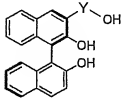
1. An asymmetric reaction catalyst obtained by mixing a pentavalent niobium compound and a triol having an optically active binaphthol derivative of R or S configuration.

2. An asymmetric reaction catalyst according to claim 1, wherein the niobium compound is represented by the following formula:

NbX_5

(wherein, X is an alkoxide or a halogen atom).

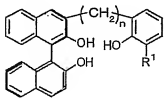
3. An asymmetric reaction catalyst according to claim 1 or 2, wherein the triol is represented by the following formula (I):



(I)

(wherein, Y represents a divalent hydrocarbon group).

4. An asymmetric reaction catalyst according to claim 1 or 2, wherein the triol is represented by the following formula (II):



(II)

(wherein, R^1 represents a hydrogen atom or a hydrocarbon group having 1 to 4 carbons; and n is an integer from 0 to 2).

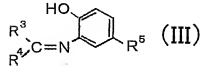
5. An asymmetric reaction catalyst according to any one of claim 1 to 4, further comprises an imidazole derivative.

6. An asymmetric reaction catalyst according to any one of claim 1 to 5, further comprises molecular sieves.

A method for preparing an optically active nitrogen-containing compound, wherein a reaction substrate represented by $R^3R^4C=N\text{-}Z$ (wherein R^3 and R^4 are selected from

the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and Z represents an aryl group or an acylamino group) and a nucleophilic agent are reacted by nucleophilic addition using an asymmetric reaction catalyst according to any one of claim 1 to 6.

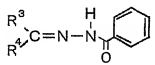
A method for preparing an optically active nitrogen-containing compound according to claim 7, wherein the above-mentioned reaction substrate is an imine represented by the following formula (III):



(III)

(wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^5 represents a hydrogen atom or a trifluoromethyl group).

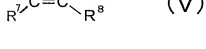
9. A method for preparing an optically active nitrogen-containing compound according to claim 7, wherein the above-mentioned reaction substrate is a benzoylhydrazone represented by the following formula (IV):



(IV)

(wherein R^3 and R^4 are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group).

10. A method for preparing an optically active nitrogen-containing compound according to any one of claim 7 to 9, wherein the above-mentioned nucleophilic agent is a silicon enolate represented by the following formula (V):



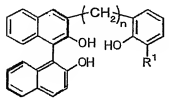
(V)

(wherein R^6 and R^7 are each independently one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, and an aromatic hydrocarbon group; R^8 is one selected from the group consisting of a hydrogen atom, an aliphatic

hydrocarbon group, an alkoxy group, and an alkylthio group; and each R^9, being the same or different, represents a hydrocarbon group).

ABSTRACT OF THE DISCLOSURE

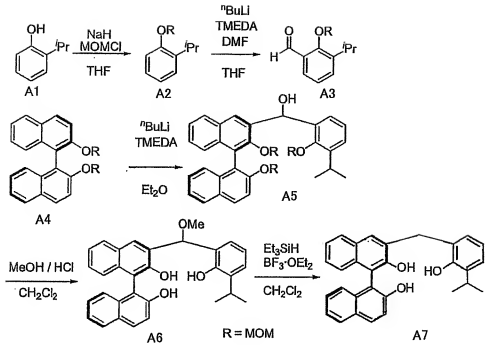
An asymmetric reaction catalyst is obtained by mixing a pentavalent niobium compound and an optically active triol or tetraol having a binaphthol structure of R or S configuration, and the triol is represented by the following formula:



(II)

(wherein, R^1 represents a hydrogen atom or a hydrocarbon group having 1 to 4 carbons; and n is an integer from 0 to 2).

Fig.1


OH
iPr
NaH
MOMCl
THF
OR
iPr
nBuLi
TMEDA
DMF
THF
O
H
OR
iPr
A1
A2
A3
OH
OR
OR
nBuLi
TMEDA
Et2O
OR
RO
OR
A4
A5
OMe
MeOH / HCl
CH2Cl2
OH
HO
OH
Et3SiH
BF3·OEt2
CH2Cl2
OH
HO
OH
A6
R = MOM
A7